



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/594,595

09/28/2006

Yukio Kato

0230-0242PUS1

5586

2292 7590 10/22/2009  
BIRCH STEWART KOLASCH & BIRCH  
PO BOX 747  
FALLS CHURCH, VA 22040-0747

EXAMINER

CHEN, SHIN LIN

ART UNIT

PAPER NUMBER

1632

NOTIFICATION DATE

DELIVERY MODE

10/22/2009

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/594,595	<b>Applicant(s)</b> KATO ET AL.	
	<b>Examiner</b> Shin-Lin Chen	<b>Art Unit</b> 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 5-14-09 & 7-23-09.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) 1-7 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 8-15 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 September 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>9-28-06, 9-28-07, 11-20-07</u> .                              | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election with traverse of group II, claims 8-15, in the reply filed on 5-14-09 and 5-14-09 is acknowledged. The traversal is on the ground(s) that groups I and II are closely related, searching one group would need to search another group, therefore, there is no undue burden to search both groups. The reference cited by Examiner does not teach each and every element of the claimed invention, so the reference does not serve to destroy the lack of unity of the claimed invention. This is not found persuasive because a search for the agent that enhances the migration and accumulation of mesenchymal stem cells does not require a search for using the agent for regeneration therapy of injured tissue. The search would not be coextensive. The putative special technical feature common to groups I and II is the agent or transplant for enhancing the migration or accumulation of mesenchymal stem cells. Fiedler et al., 2002 (Journal of Cellular Biochemistry, Vol. 87, p. 305-312) discloses that human platelet derived growth factor bb (rhPDGF-bb) can stimulate migration of primary human mesenchymal progenitor cells (MPC) in a dose-dependent manner. Therefore, there is no special technical feature contributed by the instant invention over the prior art. The element of claim 1 is the agent that enhances the migration and accumulation of mesenchymal stem cells and Fiedler does teach every element of claim 1.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5-14-09.

Art Unit: 1632

Applicants' amendment filed 9-28-06 has been entered. Claims 1-15 have been amended. Claim 16 has been canceled. Claims 1-15 are pending. Claims 8-15 are under consideration.

It is noted that since there is a supplemental reply to the restriction requirement, filed 5-14-09, that elects group II, claims 8-15, rather than group I, claims 1-7, which was elected in the original response filed 5-4-09, **the Official action mailed 6-25-09 has been vacated.**

*Priority*

3. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "EGF" in claim 12 is vague and renders the claim indefinite. The term "EGF" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Spelling out the term would be remedial.

Art Unit: 1632

The term “HB-EGF” in claim 12 is vague and renders the claim indefinite. The term “HB-EGF” is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Spelling out the term would be remedial.

The term “TGF-alpha” in claim 12 is vague and renders the claim indefinite. The term “TGF-alpha” is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Spelling out the term would be remedial.

The term “PDGF” in claim 12 is vague and renders the claim indefinite. The term “PDGF” is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Spelling out the term would be remedial.

The term “FGF” in claim 12 is vague and renders the claim indefinite. The term “FGF” is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Spelling out the term would be remedial.

The term “IGF” in claim 12 is vague and renders the claim indefinite. The term “IGF” is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Spelling out the term would be remedial.

The term “HGF” in claim 12 is vague and renders the claim indefinite. The term “HGF” is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Spelling out the term would be remedial.

6. Claims 8-15 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP

Art Unit: 1632

§ 2172.01. The omitted steps are: where the factor is administered to, and whether the injured tissue is regenerated or not.

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 8-11 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on any nucleic acid molecule, protein, peptide, antibody, small organic compound, cell or tissue that can enhance the migration and accumulation of mesenchymal stem cells in an injured tissue. The specification discloses that PDGF-BB, bFGF, HB-EGF, TGF-alpha, PDGF-AB, IGF-I, EGF, alpha-thrombin and HGF can enhance the migration and proliferation of the rabbit-derived mesenchymal stem cells (e.g. Examples 2-3).

The claims encompass various nucleic acid molecules, proteins, peptides, antibodies, small organic compounds, and cells and tissues that can enhance the migration and accumulation of mesenchymal stem cells in an injured tissue, and they are highly variant from each other and a significant number of structural differences between them are permitted. The specification fails to provide the structural features of the various nucleic acid molecules, proteins, peptides,

Art Unit: 1632

antibodies, small organic compounds, cells and tissues. Structural features that contribute to the enhancement of the migration and accumulation or suppression of diffusion of the administered mesenchymal stem cells in an injured tissue have not been disclosed. No common structural attributes identify those various nucleic acid molecules, proteins, peptides, antibodies, small organic compounds, and cells and tissues. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify those nucleic acid molecules, proteins, peptides, antibodies, small organic compounds, cells and tissues and they are highly variant, the disclosed PDGF-BB, bFGF, HB-EGF, TGF-alpha, PDGF-AB, IGF-I, EGF, alpha-thrombin and HGF in the present application are insufficient to describe the full scope of various nucleic acid molecules, proteins, peptides, antibodies, small organic compounds, and cells and tissues encompassed by the claims.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed factors. Thus, it is concluded that the written description requirement is not satisfied for the claimed factors that can enhance the migration and accumulation of mesenchymal stem cells in an injured tissue.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116).

Art Unit: 1632

With the exception of the molecules referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acid molecule, and therefore conception is not achieved regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the disclosed molecules, but not the full breadth of the claim meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

9. Claims 8-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not,

Art Unit: 1632

whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is “undue” (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The claims are directed to a method of regeneration therapy for injured tissue comprising administering at least either a factor that enhances the migration and accumulation of administered mesenchymal stem cells or a factor that suppresses the diffusion of administered mesenchymal stem cells. Claim 11 specifies the injured tissue results from osteoarthritis, bone fracture etc. Claim 12 specifies the factor as recited. Claims 13-15 specify the factor is administered topically, by injection or applied over the injured tissue.

The claims encompass various nucleic acid molecules, proteins, peptides, antibodies, small organic compounds, and cells and tissues that can enhance the migration and accumulation of mesenchymal stem cells in an injured tissue and its use for regeneration therapy for injured

Art Unit: 1632

tissues in vivo. The specification discloses that PDGF-BB, bFGF, HB-EGF, TGF-alpha, PDGF-AB, IGF-I, EGF, alpha-thrombin and HGF can enhance the migration and proliferation of the rabbit-derived mesenchymal stem cells in vitro (e.g. Examples 2-3). GFP-MSCs injected through the tail vein of rats can migrate to the calves or migrate and accumulate in greater amounts at the site where PDGF-BB was localized (Example 4).

As discussed above, the specification fails to provide the structural features of various nucleic acid molecules, proteins, peptides, antibodies, small organic compounds, cells and tissues that contribute to the enhancement of the migration and accumulation or suppression of diffusion of the administered mesenchymal stem cells in an injured tissue. Applicants apparently do NOT have possession of those various nucleic acid molecules, proteins, peptides, antibodies, small organic compounds, and cells and tissues that can enhance the migration and accumulation of mesenchymal stem cells in an injured tissue other than those proteins disclosed in the instant invention. Therefore, it is not enabled to use the claimed factor to enhance the migration and accumulation of mesenchymal stem cells in an injured tissue in vitro or in vivo without possession of those agents and transplants. Absent specific guidance, one skilled in the art at the time of the invention would not know how to use the claimed factors to enhance the migration and accumulation of mesenchymal stem cells in an injured tissue in vitro or in vivo.

The specification also fails to provide adequate guidance and evidence for how to use the claimed factors, including nucleic acid molecules, proteins, peptides, antibodies, small organic compounds, cells and tissues, for regeneration therapy of injured tissue resulted from different causes via various administration routes so as to provide therapeutic effect in regenerating the injured tissue in vivo.

Art Unit: 1632

The claims read on administering nucleic acid for regeneration therapy of injured tissue at various locations *in vivo*, therefore, the claims read on gene therapy *in vivo*. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma et al., Sept. 1997 (Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3).

The claims encompass regenerating injured tissues at various locations in a subject. Administration route plays a very important role in determining whether sufficient protein of interest can be expressed and present at the target cells at various locations *in vivo*. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) reports that numerous factors complicate *in vivo* gene transfer with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene

Art Unit: 1632

expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (e.g, bridging pages 81-82). Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy" (e.g. abstract).

The claims also read on administering numerous different proteins or peptides for regenerating injured tissue in vivo. The art of delivering a protein complex to various target sites in vivo was unpredictable at the time of the invention. The administration route includes direct injection or application, subcutaneous, intravenous, intramuscular, intraperitoneal, oral, topical, dermal, transdermal, and intranasal administration etc. There are various barriers before a protein can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, proteases and lysosomal degradation within cells, extracellular matrix between cells, gastrointestinal digestive acids, and blood-brain barrier for reaching cells in the brain. Whether the protein can reach target cells in vivo or not depends on the administration route of said protein. Hamman et al., 2005 (Biodrugs, Vol. 19, No. 3, p. 165-177) points out problems with oral administration of peptide or protein drugs. "The main reasons for the low oral bioavailability of peptide drugs are pre-systemic enzymatic degradation and poor penetration of the intestinal mucosa" (e.g. abstract). Barriers limiting the oral bioavailability of peptide drugs

Art Unit: 1632

include physical barrier, such as cell membranes and tight junctions between adjacent epithelial cells, mucus layer and efflux system, enzymatic barrier, fast elimination from the systemic circulation, the potential to develop an immune response, uptake by non-target tissues, and inefficient target cell entry (e.g. p. 166, right column). The peptide drugs administered via administration routes other than oral administration also would encounter the physical barriers as discussed and above, the enzymatic barrier, potential to develop immune response, and uptake by non-target tissues. Torchilin et al., 2003 (DDT, Vol. 8, No. 6, p. 259-266) discusses the problems of protein delivery in vivo. "The use of protein and peptide as therapeutic agents is hampered by their rapid elimination from the circulation through renal filtration, enzymatic degradation, uptake by the reticuloendothelial system (RES) and accumulation in non-targeted organs and tissues" (e.g. p. 259, right column, last paragraph). There is no evidence of record that demonstrates administration of the claimed factors via various administration routes would be able to regenerate injured tissue in any target cell in a subject. Similarly, since antibody has similar structure as protein, immunotherapy using antibody to regenerate injured tissue in vivo would encounter similar barriers as that of protein. There is no evidence of record that demonstrates administration of the any antibody via various administration routes would be able to regenerate injured tissue in any target cell in a subject.

Further, the claims encompass using various proteins or peptides for regeneration therapy of injured tissue. It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar activity or result in stabilization of the protein is extremely complex, and well outside the

Art Unit: 1632

realm of routine experimentation. Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). Davis, C. G., 1990 (The New Biologist, Vol. 2, No. 5, p. 410-419) reports that EGF repeats appears in an extraordinarily diverse group of molecules, including growth factors, transmembrane molecules, extracellular matrix proteins, and soluble secreted proteins, and it is often difficult to deduce what contribution the EGF repeat makes in a totally unrelated protein (e.g. p. 410, left column). It appears that EGF repeat can contribute to different biological functions in different amino acid contexts, i.e. different proteins.

In addition, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states “Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects” (e.g. abstract). Skolnick further states that “Knowing a protein’s structure does not necessarily tell you its function” and “Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function” (e.g. p. 36, box 2). Therefore, biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention and even same short stretch of amino acid sequence can show diverse biological functions while surrounded by different background amino acid sequences. Different proteins have different biological functions and whether a protein or a peptide can be used for regenerating injured tissue depends on the particular biological function of the protein or peptide

Art Unit: 1632

and the type of injured tissue treated. Absent specific guidance, one skilled in the art at the time of the invention would not know how to use the claimed factors to regenerate injured tissue in vivo.

It is noted that the claims only recite administering at least a factor that enhances the migration and accumulation of administered mesenchymal stem cells or a factor that suppress the diffusion of administered mesenchymal stem cells. Although the claims include the phrase “administered mesenchymal stem cells”, however, the method is missing the step of administering mesenchymal stem cells to the injured tissue and it can be interpreted that the enhancing or suppressing effect of the factor only happens when the mesenchymal stem cells are administered to the injured tissue but, in fact, the mesenchymal stem cells have NOT be administered to the injured tissue yet. Therefore, the claims read on only administering the claimed factor for regeneration therapy of injured tissue in vivo. There is no correlation between the claimed factors and regeneration of injured tissue in vivo. The specification fails to provide adequate guidance and evidence for how the claimed factor alone would be able to regenerate injured tissue in vivo via various administration routes. There is also no correlation between enhancing migration and accumulation or suppressing diffusion of mesenchymal stem cells and regeneration of injured tissue in vivo. It is unclear how migration and accumulation of mesenchymal stem cells would be able to regenerate injured tissue in vivo. Absent specific guidance, one skilled in the art at the time of the invention would not know how to use the claimed factor alone or even in combination with mesenchymal stem cells to regenerate injured tissue in vivo.

Art Unit: 1632

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

***Claim Rejections - 35 USC § 103***

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 8-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of Fiedler et al., 2002 (Journal of Cellular Biochemistry, Vol. 87, p. 305-312), Gerber et al., 2002

Art Unit: 1632

(US 20020132978 A1), Badylak et al., 2002 (US Patent No. 6,375,989 B1), or Desnoyers et al., 2008 (US Patent No. 7,456,262 B2).

The claims are directed to a method of regeneration therapy for injured tissue comprising administering at least either a factor that enhances the migration and accumulation of administered mesenchymal stem cells or a factor that suppresses the diffusion of administered mesenchymal stem cells. Claim 11 specifies the injured tissue results from osteoarthritis, bone fracture etc. Claim 12 specifies the factor as recited. Claims 13-15 specify the factor is administered topically, by injection or applied over the injured tissue.

Fiedler discloses that human platelet derived growth factor bb (rhPDGF-bb) can stimulate migration of primary human mesenchymal progenitor cells (MPC) in a dose-dependent manner. The effect of rhPDGF-bb as chemoattractive proteins for primary human MPC suggests a functional role for recruitment of MPCs during bone development and remodeling, as well as fracture healing (e.g. abstract). The mesenchymal progenitor cell is a type of mesenchyma stem cell.

Gerber teaches that the growth factor HB-EGF stimulates mesenchymal cell proliferation and migration and promotes renal epithelial cell survival (e.g. [0055]). The mesenchymal cell is “an undifferentiated cell found in mesenchyme and capable of differentiating into various specialized connective tissues” (Answers.com, mesenchymal cell). A mesenchymal cell is also a mesenchymal stem cell.

Badylak teaches growth factors FGF-2 and TGF-beta have been identified as particularly important to wound healing and tissue remodeling. FGF-2 promotes mesenchymal cell migration and proliferation to accelerate healing of gastric mucosa and calvarian bone (e.g.

Art Unit: 1632

bridging columns 15 and 16). The mesenchymal cell is “an undifferentiated cell found in mesenchyme and capable of differentiating into various specialized connective tissues”

(Answers.com, mesenchymal cell). A mesenchymal cell is also a mesenchymal stem cell.

Desnoyers teaches that hyaluronic acid (HA) is a component of skin and mesenchymal tissue where it facilitates cell migration during wound healing (e.g. bridging columns 3 and 4).

The mesenchymal cell is “an undifferentiated cell found in mesenchyme and capable of differentiating into various specialized connective tissues” (Answers.com, mesenchymal cell). A mesenchymal cell is also a mesenchymal stem cell.

Fiedler, Gerber, Badylak and Desnoyers does not specifically teach administration of rhPDGF-bb, HB-EGF, FGF-2 or HA to injured tissue for regeneration therapy, administered simultaneously, continuously or separately, or administered topically, by injection or by applying over the injured tissue.

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to use the rhPDGF-bb, HB-EGF, FGF-2 or HA for regeneration therapy of injured tissue because Fiedler teaches that rhPDGF-bb can stimulate migration of primary human mesenchymal progenitor cells (MPC) in a dose-dependent manner, Gerber teaches HB-EGF stimulates mesenchymal cell proliferation and migration and promotes renal epithelial cell survival, Badylak teaches FGF-2 promotes mesenchymal cell migration and proliferation to accelerate healing of gastric mucosa and calvarian bone, and Desnoyers teaches that hyaluronic acid (HA) facilitates cell migration during wound healing. It is noted that the claims only recite administering the factor for regeneration therapy of injured tissue, whether the injured tissue is regenerated or not is irrelevant, therefore, the claims are obvious to one of ordinary skill in the

Art Unit: 1632

art in view of the teachings of Fiedler, Gerber, Badylak and Desnoyers. It also would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to administer the claimed factor at different time schedule or different administration routes because determining effective administration schedule or administration route of the factor is routine optimization of a result-effective variable and is obvious to a person of ordinary skill.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to use the factor for recruitment of MPCs during bone development and remodeling, as well as fracture healing as taught by Fiedler or to use the factor for wound healing and tissue remodeling as taught by Badylak with reasonable expectation of success.

### ***Information Disclosure Statement***

13. The references cited in the information disclosure statement filed 9-28-06 are duplicates of the references cited in the information disclosure statement filed 9-28-07. Further, the references cited in the information disclosure statement filed 11-20-07 are duplicates of the references cited in the information disclosure statement filed 9-28-07. Therefore, the information disclosure statements filed 9-28-06 and 11-20-07 will not be considered. It has been placed in the application file, but the information referred to therein has not been considered as to the merits.

### ***Conclusion***

No claim is allowed.

Art Unit: 1632

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.  
/Shin-Lin Chen/  
Primary Examiner  
Art Unit 1632